Pregnancy Outcomes following Preconception, Early and Late Administration of Vaginal Micronized Progesterone for Recurrent Pregnancy Loss

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Abstract

Objectives: *Pregnancy outcome following preconception to 36th week of pregnancy treatment with vaginal micronized progesterone (VMP) for recurrent pregnancy loss.*

Methods: *We prospectively analyzed 96 cases divided in three groups (differentiated by the moment of two previous pregnancy losses): 32 cases - group A - during the first trimester, 6 cases - group B - during the third trimester [treated with Folic Acid (FA), 200 mg/day VMP (14 days/month, luteal phase), continued after positive pregnancy test until 36th week], and 58 cases in the control group (C) on placebo.*

Primary outcomes included: *time to conceive, gestational age at miscarriage/preterm birth, birthweight, Apgar scores, congenital malformations, composite neonatal morbidity, oxygen supplementation, mechanic ventilation. Secondary outcomes included: stillbirth, newborn death before discharge, maternal weight gain, maternal morbidity; hospitalization for threatened abortion/preterm birth.*

Statistics analysis: *Student t test /ANOVA.*

Results: *Primary outcomes: fetal weight: controls: 2506.1±699.21g, group A: 3100 ± 489.41g (P=0.001 vs. control); group B: 3216 ± 537.27 g (P=0.022 vs. control); Apgar Scores: 1/5 minutes: controls: 8.05 ± 1.98/ 8.2 ± 1.99, group A: 8.45 ± 1.53 (P=0.40 vs. control)/8.77 ± 1.11 (P=0.21 vs. control), group B: 4.83 ± 4.57 (P=0.14 vs. control) / 4.83 ± 4.62 (P=0.13 vs. control); umbilical cord blood pH when Apgar <7/5 minutes: controls: 7.20 ± 0.19, group A :7.14 ± 0.34 (P=0.81 vs. control), group B : 6.55 ± 0 (P=0.0001 vs. control). GA at delivery: 24-28 weeks (0/0/2 in group A/B/C); 29-34 weeks (1/1/16 in group A/B/C); ≥ 35 weeks (21/5/23 in groups A/B/C). Malformations: 2 hypospadias (group A, control), 1 cryptorchidism, 1 hydrocele, 1 umbilical hernia (control); Neonatal morbidity: Respiratory Distress Syndrome: 2/1/5 (group A/B/C), no: BPD, IVH, NEC.*

Secondary outcomes: *25 miscarriages; 4 fetal deaths before discharge (0/2/2-group A/B/C); maternal weight gain: control: 11.95 ± 4.75, group A:16.77 ± 5.71 (P=0.001 vs. control), group B: 14.33 ± 3.32 (P=0.24 vs. control) gestational hypertension [group B: 2 (7.1%), controls: 3 (19%)], no gestational diabetes; hospitalization for threaten abortion (8 vs. 20 controls)/ preterm birth (10 treated vs. 18 controls).*

Conclusion: *The study suggest that VMP preconception to 36 weeks gestation in recurrent pregnancy loss is followed by reduction of: preterm birth before 34 weeks (13.6% treated vs. 36.6% controls), miscarriages (23.7% treated vs. 27,7% controls), increased birthweight (P=0.001, group A; P=.022 group B), less reduction of umbilical cord blood pH (P=0.0001- group B) when Apgar score <7/5 minutes, less neonatal morbidity (only RDS: 10.3% treated vs. 12.2% controls), insignificant difference in perinatal mortality; less fetal abnormalities, lower incidence of gestational hypertension (5.2% treated vs. 19% controls), no gestational diabetes, and hospitalization for miscarriage (28.6% treated vs. 48.8% controls), or preterm birth threaten (35.1% studied vs. 43.8% controls).*

Keywords: *progesterone, miscarriage, preterm birth, neonatal morbidity/mortality*

Introduction

Infertility, miscarriage and preterm birth, gestational pathology, neonatal morbidity and mortality continue to be problematic for medical staffs all over the world; the medical history records many attempts to change the situation. In the last 40-50 years progestin and progesterone derivatives have been administered during reproductive years for several reasons: luteal phase support when luteal phase defect or inadequate corpus luteum; spontaneous pregnancy achievement or IVF treatment[1]; threatening miscarriage, recurrent miscarriage[2], prevention of preterm labor[3].

Objectives:

We investigated the pregnancy outcome following preconception to 36th week of pregnancy treatment with 200 mg/day vaginal micronized progesterone (VMP) for recurrent pregnancy loss.

Material and methods

We prospectively analyzed 96 subjects divided in three groups (differentiated by the moment of two previous pregnancy losses): 32 subjects - group A - during the first trimester, 6 subjects - group B - during the third trimester [early preterm birth with neonatal death or stillbirth, treated with FA, 200 mg/day VMP (14days/month, luteal phase), continued after positive pregnancy test until 36th week], and 58 subjects in the control group (C) on placebo.

The patients were diagnosed and enrolled in two university clinics of Obstetrics from "Carol Davila" University of Medicine and Pharmacy, Bucharest: "Dr I. Cantacuzino" and "St. Pantelimon", if they met all inclusion/exclusion criteria.

The inclusion criterion was the existence of two pregnancy losses (in the first or third trimester).

The exclusion criteria were: major uterine malformations, subtle ovulatory dysfunction, as that related to hyperprolactinemia; positive tests for: toxoplasmosis, listeriosis, CMV, syphilis; major chronic medical diseases (e.g.: insulin-necessitating diabetes mellitus or pharmacologically treated hypertension), treatment with 10.000 or more units of unfractionated heparin per day, treatment with low-molecular-weight heparin at any dose or other diagnosed blood coagulation protein or platelet defects; previous pregnancies with chromosomal abnormalities as numeric abnormalities (aneuploidies) and structural anomalies (defects in the structure of 1 or more chromosomes); previous gestation over 42 weeks with fetal wastage. All cases were ultrasonically assessed between 12 and 20 weeks+6 days of gestation (to confirm the duration of gestation, to screen for major fetal anomalies, to diagnose ultrasonic large/restricted fetus) and between 32 and 34 weeks (to assess fetal growth).

Results

Primary: time to conceive, moment of miscarriage, time until delivery: preterm birth before 32 and 37 weeks, birthweight, Apgar scores, congenital malformations, composite neonatal morbidity rate, containing severe respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), oxygen supplementation, mechanic ventilation, death before discharge, length of admission in NICU.

Table 1

Patients characteristics

		Group A n=32	Group B n=6	Group C (control) n=58
Full term delivery		22	6	41
Miscarriages		10	0	17
Age (range) yrs		31.33 ± 4.54 p=0.038	31.33 ± 4.54 p=0.038	26.9 ± 4.77
Gestation	=2	10	1	9
	>2	22	5	32
Parity	1	12	3	5
	2	9	2	4
	>2	1	1	7
Height (cm) Range (limits)		160.8 (155-168)	160.5 (155-164)	158.8 (155-165)
Preconception Weight (kg)		58.59 ± 9.27 p=0.13	61.33 ± 12 p=0.09	55.32 ± 7.39

P - values when groups are compared versus control

Table 2

Primary pregnancy outcomes

		Group A	Group B	Group C
Time to conception	≤6 months	27 (86%)	5 (83.3%)	36 (60.7%)
	>6 months	5 (15.6%)	1 (16.6%)	22 (37.9%)
Gestational age if miscarriage	<12 wks	7 (21.9%)	0	13 (22.4%)
	13-23 wks	3 (9.3%)	0	4 (7.2%)
Gestation Age at Delivery	24-28 wks	0	0	2 (4.8%)
	29-34 wks	1 (4.5%)	1 (16.6%)	16 (39%)
	≥35 wks	21 (96.5%)	5 (83.4%)	23 (56%)

Table 3(a)

Infant outcome

		Group A n=22	Group B n=6	Controls n=41
Fetal weight (g)		3100 ± 489.41 p=0.001	3216 ± 537.27 p=0.022	2506.1 ± 699.21
Fetal weight (g)	<1500g	0	0	4
	<2500g	1 p=0.0001	0	16
Apgar Score	-1 min	8.45 ± 1.53 p=0.40	4.83 ± 4.57 p=0.14	8.05 ± 1.98
	-5 min	8.77 ± 1.11 p=0.21	4.83 ± 4.62 p=0.13	8.2 ± 1.99
pH blood cord when Apgar	<7/5'	5 cases	2 cases	15 cases
	<7.20	3	2	4
	7.21-7.24	0	0	5
	≥7.25	2	0	6
Malformations	Hypospadias	1	0	1
	Criptorhydia	0	0	1
	Hydrocele	0	0	1
	Umbilical hernia	0	0	1
Composite Neonatal Morbidity	RDS	2	1	5
	BPD	0	0	0
	IVH	0	0	0
	NEC	0	0	0

RDS - Respiratory Distress Syndrome, BPD - Bronchopulmonary Dysplasia, IVH - Intraventricular Hemorrhage, NEC - Necrotizing Enterocolitis

Table 3(b)

Infant outcomes

		Group A 22	Group B 6	Group C (Controls) 41
Need for oxygen supplementation		3 (13.6%)	1 (16.6%)	25 (61.2%)
Mechanical ventilation		2 (4.5%)	1 (16.6%)	5 (12.1%)
Length of admission in the NICU (days)	< 7 days	0	0	5 (12.1%)
	> 7 days	2 (4.5%)	1 (16.6%)	5 (12.1%)

Secondary outcomes: maternal weight gain, maternal morbidity (gestational diabetes, gestational hypertension); hospitalization for threatened miscarriage/ preterm birth.

Statistical analysis. Student t test was used for comparison of each group of treated patients to controls (P value), P<0.01 was considered statistical significant.

Results. Groups A and B were treated for 6 months before conception with vaginal micronized progesterone 200 mg/d (14 days/month, each night, from the 14th day of menstrual cycle), continued immediately after a positive pregnancy test (the 7th-10th days of amenorrhea) and prolonged till the 36th

Table 4

Pregnancy secondary outcomes

		Group A 22	Group B 6	Controls 41
Infant outcomes				
Stillbirth		0	1 (16.6%)	2 (5%)
Fetal deaths before discharge		0	0	2 (4.4%)
Maternal outcomes				
Maternal weight gain (range) kg		16.77 ± 5.71 p= 0.001	14.33 ± 3.32 p= 0.24	11.95 ± 4.75
Gestational Hypertension		0	2 (33%)	3 (19%)
Gestational Diabetes		0	0	0
Hospitalization for threatened miscarriage	<12 wks	10 (31.2%)	1 (16.6%)	24 (41.4%)
	13-24 wks	12 (37.5%)	2 (33%)	36 (62%)
Hospitalization for threatened preterm birth	25-28 wks	2 (9%)	0	11 (26.8%)
	29-34 wks	10 (45%)	0	20 (48.7%)
	35-37 wks	2 (9%)	1 (16.6%)	8 (19.5%)

week of gestation; the control group (58 patients) was treated during pregnancy with non a specific antispastic muscle-relaxant mixture, when necessary. Table 1 presents patients' characteristics: age, gestation, parity, height, preconception weight, and weight gain.

Regarding the pregnancy's primary outcomes (Table 2): the time to conceive was analyzed around six months: the treated patients conceived earlier than controls (86% - group A, 83.3% - group B vs. 36% controls), gestational age in case of miscarriage was analyzed before 12 weeks and between 13 and 23 weeks: within treated subjects there were no miscarriages in group B, and for group A (the first trimester) we recorded 7 (21.9%) vs. 13 (22.4%) in controls, and (for the second trimester) we recorded 3 (9.3%) vs. 4 (7.2%) in controls. Gestational age at delivery was analyzed at 24-28 weeks, 29-34 weeks, ≥35 weeks: during 24-28 weeks there was no case in treated vs. 2 (4.8%) in controls; between 29 and 34 weeks there was 1 case (4.5%)- group A, 1 (16.6%) - group B and 16 (39%) in controls.

Regarding the infants' outcome (Tables 3a and 3b) we analyzed the fetal weight globally and per categories: below 1,500 g and 2,500 g; the treated patients delivered heavier babies than the controls, no baby below 1,500 g and only one baby below 2,500 g in group A vs. 16 in controls. The Apgar scores at 1 and 5 minutes were better for newborns of treated mothers than those in control groups, but not statistically significant; the acidemia when Apgar score <7 was registered more frequent in babies of control groups than in treated ones. The number of malformations was higher amongst controls (one case of hypospadias, criptorhydia, hydrocele, umbilical hernia vs. one case of hypospadias in group A). The composite neonatal morbidity was represented only by respiratory distress syndrome with 2 (group A), 1 (group B), and 5 (controls) subjects.

Amongst infant outcomes we analyzed the need for special neonatal care requirements like oxygen supplementation (more cases in controls 61.2% vs. 13.6% in group A and 16.6% in group B), mechanical ventilation (more cases in controls 12.1% vs. 4.5% in group A, 16.6% in group B). The duration of admission in NICU was discussed in the terms of less or more 7 days: the babies of control mothers had a longer duration of admission in NICU [5 (12.1%) vs. 2 (4.5%) - group A and 1 (16.6%) - group B]

Secondary outcomes for pregnancy (Table 4): if the number of stillbirth is not so different between groups (2 in controls vs. 0 in group A and 1 in group B), the fetal death before discharge is registered only in controls (2 - 4.4%).

Regarding maternal health during pregnancy, we documented a more important maternal weight gain in treated vs. control groups (p<0.001 - group A), more cases with gestational hypertension in control group (3 vs. 2 in group B), no case of gestational diabetes mellitus; less cases of maternal hospitalization for threaten miscarriage

in treated (10 group A and 1 group B vs. 24 cases in control group in the first trimester; 12 group A, 2 in group B vs. 36 cases in control group between 13-24 weeks) and for threatened preterm birth at 25-28 weeks (2 in group A vs. 11 in control group), at 29-34 weeks (10 in group A vs. 20 in control group), and at 35-37 weeks (2 in group A, 1 in group B vs. 8 in control groups).

Discussions

The use of progesterone and progestin derivatives in reproduction has been discussed throughout the past 40-50 years, and only two formulations are now considered safe: natural progesterone administered vaginally (either as a pessary or as a cream), and a synthetic caproate ester of naturally-occurring 17-alpha-hydroxyprogesterone (administered as a long-acting intramuscular injection). There are some differences regarding their intended beneficial effects on becoming pregnant and/or pregnancy outcome.

Micronized progesterone is the sole natural progesterone formulation available in Romania (dydrogesterone being a semi-synthetic product), and the vaginal route of administration ensures better bioavailability of progesterone in the uterus (10 times higher than for i.m. administration) and minimal systemic undesirable effects[4,5,6,7] because of a first-pass uterine effect, explained by direct diffusion through tissue, intracervical aspiration, absorption into venous or lymphatic circulatory systems, and countercurrent vascular exchange with diffusion from utero-vaginal veins/lymph vessels to arteries.

In our study the maternal age of treated patients was higher than in controls (31.33 ± 4.54 vs. 26.9 ± 4.77; P= 0.038), and Devoto L, Vega M, Kohen P, et al (2002) (8) have demonstrated that when aging the molecules linked to the apoptosis of corpus luteum (pro-inflammatory cytokines, reactive oxygen species, steroids and inducible nitric oxide synthetase) increase and induce preferentially a decrease of progesterone biosynthesis in mid and late luteal cells (in cultures).

Progesterone supplementation before conception modulates the contractility of fallopian tubes and myometrium for gamete/embryo transportation throughout the utero-tubal cavities and successful embryo implantation in spontaneous and/or assisted reproduction[9,10,11,12,13,14] and maintains decidual viability[15]; besides that, the joint effects of progesterone and estrogens lower the vascular resistance within the uterine circulation and increase the embryo implantation rate due to certain effects on endometrial stroma cells influencing various cytokine profiles (deemed as a response of the female reproductive system to paternal histocompatibility antigens (MHC), since the uterus has certain immune "privileges" during pregnancy).

In this study the progesterone supplementation before conception, administered during the luteal phase, was associated to an immediate conception rate (in less than 6 months) of 86%, and 83.3% in groups A and B respectively vs. 60.7% in controls; this supplementation was continued as soon as the β-hCG pregnancy test was positive (7 to 10 days after fertilization).

Progesterone enhances the local production of Th2 and/or Leukemia Inhibiting Factor (LIF) cytokines, which may contribute to preserving the pregnancy. The defective decidual production of LIF, M-CSF, Il-4, IL-10 and/or Th2 type cytokines may contribute to the development of unexplained recurrent abortions[16,17,18].

The protocol of this study sustains corpus luteum; both early and late pregnancy by vaginal micronized progesterone supplementation [in cases at high risk for recurrent pregnancy loss[19]] have used either the luteal protocol or the first trimester protocol in IVF pregnancies, showing that for the luteal protocol the miscarriage rate was higher than for the first trimester protocol, while the live birth rate was better (76.8% luteal protocol vs. 75.0% first trimester protocol; P=0.80).

Manno M, Marchesan E, Cicutto D, et al (2005) (13) have shown in a retrospective study that vaginal progesterone induced greater implantation and pregnancy rates than intramuscular supplementation for intracytoplasmic sperm injection, but not for in vitro fertilization cycles.

Progestin/Progesterone derivatives suppress Thrombin- and Il-1{beta}-Induced Il -11, associated with preterm delivery, abruptio placentae and chorioamnionitis. IL-11 is a cytokine with pleiotropic biological effects, including the induction of Th-2 type and the inhibition of Th-1 type cytokine responses; it paradoxically enhances the prostaglandins synthesis, which induces labor.

Progesterone/17alpha-hydroxyprogesterone are administered for miscarriage and preterm birth prevention at different pregnancy ages; at 16-20 weeks[20], according to the National Institute for Child Health and Human Development, 17 alpha-hydroxyprogesterone reduced the rate of delivery before 32 wks from 18.6% to 11.4% (P: 0.018), and before 35 weeks - from 30.6 to 20.6 % (P=0.0165); at 24-34 weeks, micronized progesterone reduced the rate of delivery before 34 weeks from 34% to 19%. According to the protocol of this study, micronized progesterone was administered before conception to 36 weeks and the delivery rate after 35 weeks increased from 56% in controls to 96.5%[21,22,23,24,25].

Conclusions

Vaginal micronized progesterone administered before conception (in early and late pregnancy) for recurrent pregnancy loss results in:

- Less time to conceive (less than 6 months: 81.3 % studied vs. 60.7% control).
- A reduction of miscarriages (23.7% treated vs. 27.7% control).
- A significant reduction of preterm birth (before 34 weeks: 13.6% treated vs. 36.6% control).
- An increase of birthweight (P=0.001, group A; P=0.022 group B), less cases with reduced blood cord pH (p=0.0001 - group B) when Apgar score <7/5 minutes,
- Fewer cases requiring oxygen supplementation (10.5% vs. 61.2%) or mechanical ventilation (7.6% studied vs. 12.1% control).
- Lesser NICU admission days (>7 days: 7.6% studied vs. 12.1% control).
- Lower neonatal morbidity (only RDS: 10.3% treated vs. 12.2% controls), and a non-significant difference in perinatal mortality.
- 2 cases with hypospadias (group A, controls), many other abnormalities in controls.
- Lower incidence of gestational hypertension in treated (5.2%) vs. controls (19%), and no gestational diabetes.
- Less hospitalization for threatened abortion (28.6% treated vs. 48.8% controls), and for preterm birth (35.1% studied vs. 43.8% control). ■

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